

The Role of Cow's Milk Protein In Children with Chronic Functional Constipation

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STATEMENT OF ORIGINALITY

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Data collection task assignment

Data collection task	Completed by
Introduction of the study to potential participants	Paediatrician or paediatric continence nurse
Collection of medical history	Paediatrician or paediatric continence nurse
Collection of nutritional assessment data	Dietitian researcher (EC) and research assistant dietitian (3 participants only)
Laboratory analysis of blood samples	HAPS and New England pathology
Laboratory analysis of faecal samples	HAPS and New England Pathology
Entry of data into computer data base	Research assistant
Analysis of nutritional assessments, constipation diaries, blood test result, faecal test reports	Dietitian researcher (EC)

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Glossary of abbreviations used in this thesis

AIS	Australian Illawara Shorthorn Cattle
ALT	Alkaline phosphatase
ANOVA	Analysis of Variance
AntiDNase B	Antideoxyribonuclease B titre
AST	Aspartate Amino Transferase
ASO	Antistreptolysin O
ASOT	Antistreptolysin O titre
β -casein	β -casein
BCM7	Beta-casomorphin-7
CMP	Cow's Milk Protein
CFC	Chronic Functional Constipation
CMPA	Cow's Milk Protein Allergy
CMPI	Cow's Milk Protein Intolerance
Dx	Diagnosis
(EC)	Elesa Crowley
ELISA	Enzyme linked immunosorbent assay
ESR	Estimated Sedimentation Rate
FBC	Full Blood Count
GIT	Gastrointestinal Tract
GGT	Serum Gamma Glutamyl Transpeptidase
hr	hour
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
invent	invention
intol	intolerance

LFT	Liver Function Test
longitud	Longitudinal
M	Male
NHMRC	National Health and Medical Research Council
Ob	observation
%	percentage
PCR	Protein C reactive test
+ ve	positive
RAST	radioallergosorbent tests
RCC	red cell count
RCT	Randomised Controlled Trial
SIDS	Sudden Infant Death Syndrome
Th1	T helper 1 cells
Th2	T helper 2 cells
TNF- α	Tumor Necrosis Factor [alpha]
WBC	White Blood Cell
wk	week
WCC	white cell count

Synopsis

The idea for this research came from a problem identified in my practices as a clinical dietitian. My interest in cow's milk β casein A2 was sparked after discussion with Professor Tim Roberts, from The University of Newcastle, who described previously cow's milk allergic people who are able to tolerate the consumption of cow's milk β casein A2, without symptoms reoccurring.

The goal of this thesis is to report on research that explored the role of cow's milk protein in children with chronic functional constipation. The research consisted of a systematic review of the literature, two clinical crossover trials, and a qualitative exploration of the lived experience of following a milk-free diet.

Chapter 1 provides the introduction to both allergy and constipation, and the relationship between the two. Causes of constipation can be organic or functional (1). Organic causes of constipation occur in relation to a primary disease classification such as endocrine or metabolic disorders, neurologic disorders, anatomic malformation, collagen vascular disease and some drugs (for example, opiates). Chronic functional constipation is defined as having one bowel motion every three to 15 days (2) and is characterised by painful bowel movements or strain in defecation, hard stools with increased diameter or pellets, and occurs with or without soiling (3). This functional constipation is defined as chronic when it persists for greater than two weeks (4).

Chapter 2 details the methods used in searching the literature for evidence for a role of cow's milk consumption in chronic functional constipation in children from 1980 to 2006. This was published as a systematic review. The literature surrounding cow's milk and constipation was found to be limited. None of the studies previously conducted were population-based or structured to provide evidence-based evaluation or treatment guidelines at either the general practitioner or paediatric specialist level. The strongest evidence found was a double blind

randomised control trial conducted by Iacono and colleagues (3). The research study by Iacono and colleagues (3) provides evidence of an association between cow's milk and constipation. The following research questions were developed from the systematic review:

1. Can the results of the Iacono and colleagues study of children with chronic functional constipation that respond to the replacement of cow's milk protein with soy be replicated in the Australian setting?
2. Does cow's milk β casein A1 cause constipation in children with chronic functional constipation?
3. What are the immunological and biochemical mechanisms underlying chronic functional constipation that respond to the removal of cow's milk protein in children?
4. What factors affect the feasibility of parents administering a cow's milk protein free diet to their children?

The four questions were addressed by two different dietary crossover trials and a qualitative study.

Chapter 3 describes the participants recruited and the methods used for the crossover trials investigating milk protein and paediatric chronic functional constipation including details of the primary outcome measure (number of bowel motions during a two-week trial period) and secondary outcome measures (biochemical, immunological and faecal analysis).

Chapter 4 describes the results of Trial 1, which replicated the Iacono and colleagues study in the Australian setting, investigating the effects of soy and cow's milk β -casein A1 in children with chronic functional constipation. One hundred percent of participants experienced resolution of their constipation during the soy

milk condition compared with 68% experiencing resolution during the soy milk condition in the Iacono and colleagues study (n=65). Thirteen participants were recruited to Trial 1. Nine participants returned constipation diaries for the study period. The mean (SD) number of stools for each of the conditions was: baseline, 5.1 (1.4); cow's milk 9.9 (4.4); washout 13.0 (5.2); and soy milk 15.1 (5.0). The differences between the three dietary conditions were statistically significant, $p=0.03$. The results confirmed the hypothesis that children in the Australian setting with chronic functional constipation unresponsive to the usual treatments, respond to the removal of cow's milk protein from the diet.

Chapter 5 describes the results of Trial 2, the double blind crossover trial comparing the effects of cow's milk β -casein A1 and cow's milk β -casein A2 in children with chronic functional constipation. Thirty-nine participants were recruited to Trial 2 and 26 participants returned constipation diaries for the trial period. Unlike the soy result, the cow's milk β casein A2 did not give 100% resolution of constipation, in fact, the percentage resolution was almost identical to the cow's milk β casein A1 result. The fact that some children responded during the cow's milk casein A1 condition in both trials could be caused by a threshold effect, given it was likely that participants were consuming less cow's milk protein during the trial (400 mL with elimination of all other sources of cow's milk protein) than on their pre-trial diet. Resolution with both the cow's milk β casein A1 and cow's milk β casein A2 conditions suggests that these children are able to tolerate some cow's milk protein before the symptom of constipation occurs. This could be a food intolerance type reaction or there is some other component in cow's milk that is causing the problem in these children.

Chapter 6 describes a qualitative study of the feasibility for mothers to administer a cow's milk protein free diet to their children. The experiences of mothers following a cow's milk protein free diet to assist in the management of chronic functional constipation in children were reported. A number of themes were identified that are

useful to health professionals educating families. Mothers found the removal of cow's milk protein from the diets of their children challenging but persevered due to the potential benefit to their children. Many mothers planned to continue post study with a modified approach to the cow's milk protein free diet by allowing some cow's milk protein in the diet to make the diet more acceptable to the family but not as much as the pre-trial diet. These experiences provide health professionals with valuable insights and ideas to assist their patients to manage a cow's milk protein free diet.

Chapter 7 discusses all aspects of the research including any limitations. The results of Trial 1 confirmed the hypothesis that children in the Australian settling with chronic functional constipation unresponsive to the usual treatments respond to the removal of cow's milk protein from the diet. Therefore, cow's milk protein is involved in the aetiology of constipation in these children. All the study participants demonstrated an absence or low level of normal gut flora, which may affect bowel regularity. Further research into species present and absent may provide further explanations to the lack of bowel regularity in these children.

The immunological and biochemical mechanisms underlying chronic functional constipation that respond to the removal of cow's milk protein requires further investigation. Although the number of statistically significant variables between the conditions was low, there was a high degree of abnormality. Further investigations are needed, including research into food intolerance reactions that affect the nerve endings in the bowel. The results in Trial 1 and Trial 2 are suggestive of an involvement of blood factors including platelets and monocytes. Other children may have a chronic *Streptococcus A* infection which may be contributing to constipation as well as to liver function abnormalities. Liver function abnormalities were observed for some participants in both trials, independent of milk condition.

The extent to which the research questions have been answered is evaluated in Chapter 7, which includes the conclusions and recommendations of this research. In brief, the findings were:

- Children with chronic functional constipation that is unresponsive to the traditional treatments should trial a cow's milk protein free diet for at least two weeks to determine whether this may resolve the constipation. During this period, the numbers and form of bowel motions should be recorded and results compared to a one week record collected prior to commencing the cow's milk protein free diet.
- Due to the complicated nature of a cow's milk protein free diet, especially the number of processed foods which contain hidden cow's milk protein, consultation with a dietitian is essential for implementation of this diet. The dietitian should consider educating the patient's family, both parents and siblings, to ensure the best outcome in terms of acceptance and compliance of the diet, and provide adequate resources.
- If this dietary modification is successful for the child and alleviates constipation, consultation with a dietitian is recommended to determine the amount tolerated and nutritional adequacy of the diet. Soy milk is recommended as a substitute for cow's milk and a probiotic needs to be prescribed to assist with the normalisation of gut flora.
- Education of health professionals such as general practitioners, paediatricians, and paediatric continence nurses, regarding a cow's milk protein free diet for chronic functional constipation, is essential to support the child and his/her family and integral to the success of this strategy. The findings of this research will be published in the scientific literature and as conference presentations.

It is hoped that these findings will assist in the management of children with chronic functional constipation unresponsive to the traditional treatments.